EFFICACY OF FAVIPIRAVIR AND MOLNUPIRAVIR AGAINST NOVEL SARS-COV-2 VARIANTS *IN VITRO* AND *IN VIVO*

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The COVID-19 disease pandemic remains a significant global problem, resulting in hundreds of millions of cases and millions of deaths. The search for specific inhibitors of SARS-CoV-2 for the treatment of this infection remains relevant. Drugs such as Favipiravir and Molnupiravir, which exhibit specific antiviral activity against SARS-CoV-2, are already being used to treat patients. However, there is limited evidence of their effectiveness, especially against novel genetic variants of the COVID-19 pathogen. The aim of this study was to investigate the antiviral effect of these drugs using an *in vitro* experimental model of SARS-CoV-2 infection in Vero E6 cell culture and an animal model of infection using Syrian hamsters. It has been established that Molnupiravir has an inhibitory effect against variants of the SARS-CoV-2 with IC50 values from 16.51 to 7.88 μM *in vitro*, and reduces the infectious titer of the virus in the lungs of animals by ~1.5 Log10 *in vivo*, in while Favipiravir shows lower activity and severe toxicity. Dose selection and frequency of use remain unexplored.

Keywords: COVID-19, SARS-CoV-2, antiviral activity, Favipiravir, Molnupiravir, Omicron, antivirals

Funding: the study was supported by the Russian Ministry of Health, grant № 121111200070-4 (P16).

Acknowledgments: the authors would like to thank the staff of N.I. N.F. Gamaleya A. Zakharova and T. Remizov for organizing the supply of reagents for the study.

Author contribution: Sinyavin AE — design of the experiment, study of antiviral activity, data analysis, writing the text; Russu LI — work with the virus and animals; Vasina DV — work with animals; Shidlovskaya EV, Kuznetsova NA — PCR analysis, data processing; Gushchin VA — research supervision, text editing; Gunzburg AL — approval of the research concept.

Compliance with ethical standards: the study was approved by the ethics committee of the Federal State Budgetary Institution "N.N. N.F. Gamaleya" of the Ministry of Health of the Russian Federation (protocol № 27 of June 6, 2022); conducted in compliance with the principles of the Declaration of Helsinki of the World Medical Association.

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Received: 05.12.2022 **Accepted:** 20.12.2022 **Published online:** 31.12.2022

DOI: 10.24075/brsmu.2022.071

ЭФФЕКТИВНОСТЬ ФАВИПИРАВИРА И МОЛНУПИРАВИРА ПРОТИВ НОВЫХ ВАРИАНТОВ SARS-COV-2 В СИСТЕМАХ *IN VITRO* И *IN VIVO*

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Пандемия заболевания COVID-19 остается важной глобальной проблемой общественного здравоохранения, которая приводит к сотням миллионов случаев заболевания и миллионам летальных исходов. По всему миру активно идут разработка и исследования специфичных ингибиторов SARS-CoV-2 для лечения данной инфекции. Такие препараты, как фавипиравир и молнупиравир, проявляющие специфичную противовирусную активность против SARS-CoV-2, уже применяют для лечения пациентов. Однако имеются ограниченные данные об их эффективности, особенно против новых генетических вариантов возбудителя COVID-19. Целью исследования было изучить противовирусный эффект этих препаратов с использованием экспериментальной модели инфекции SARS-CoV-2 на культуре клеток Vero E6 *in vitro* и животной модели инфекции с использованием сирийских хомячков. Установлено, что молнупиравир оказывает выраженное ингибирующее действие против различных вариантов вируса SARS-CoV-2 со значениями IC50 от 16,51 до 7,88 μM *in vitro* и снижает инфекционный титр вируса в легких животных на ~1,5 Log10 *in vivo*, в то время как фавипиравир проявляет более низкую активность и выраженную токсичность. Полученные результаты указывают на необходимость дальнейших исследований в направлении подбора дозировок и кратности применения.

Ключевые слова: COVID-19, SARS-CoV-2, противовирусная активность, фавипиравир, молнупиравир, Омикрон, антивирусные препараты

Финансирование: исследование выполнено при финансовой поддержке Минздрава России, грант № 121111200070-4 (П16).

Благодарности: авторы выражают благодарность сотрудникам НИЦЭМ им. Н.Ф. Гамалеи А. Захаровой и Т. Ремизову за организацию поставки реагентов для исследования.

Вклад авторов: А. Э. Синявин — планирование эксперимента, исследование противовирусной активности, анализ данных, написание текста; Л. И. Руссу — работа с вирусом и животными; Д. В. Васина — работа с животными; Е. В. Шидловская, Н. А. Кузнецова — ПЦР-анализ, обработка данных; В. А. Гущин — руководство исследованием, редактирование текста; А.Л. Гинцбург — утверждение концепции исследования.

Соблюдение этических стандартов: исследование одобрено этическим комитетом ФГБУ «НИЦЭМ им. Н.Ф. Гамалеи» МЗ РФ (протокол № 27 от 6 июня 2022 г.); проведено с соблюдением принципов Хельсинкской декларации Всемирной медицинской ассоциации.

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Статья получена: 05.12.2022 **Статья принята к печати:** 20.12.2022 **Опубликована онлайн:** 31.12.2022

DOI: 10.24075/vrgmu.2022.071

The COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to pose a global public health threat and increase the economic burden. The spread of the virus in humans is still ongoing, and new variants of SARS-CoV-2 are constantly emerging, leading to an urgent need for drugs to treat this disease, as well as for expanded studies on the effectiveness of approved treatments for COVID-19.

For the treatment of COVID-19 in the Russian Federation, it is recommended to use several drugs with a specific antiviral effect, including Favipiravir and Molnupiravir. But the efficacy of these drugs for new variants of SARS-CoV-2 remains unknown.

The broad-spectrum antiviral drug Favipiravir [1] targets the viral RNA-dependent RNA polymerase (RdRP). It is effective against both seasonal virus and avian influenza, as well as SARS-CoV-2 in cell culture and *in vivo* in experimental animal models. In humans, Favipiravir is phosphorylated by cellular enzymes to its active form, Favipiravir-ribofuranosyl-5'-triphosphate (F-RTP). F-RTP does not greatly affect on cellular transcription. There are several hypotheses regarding how F-RTP interacts with RdRp. Some studies have shown that when F-RTP incorporated into the nascent RNA strand, it prevents RNA strand elongation and virus replication. It has also been shown, that the presence of purine analogues can reduce the antiviral activity of Favipiravir, i.e., competition between F-RTP and purine nucleosides for binding to RdRp is possible. According to the results of clinical studies, Favipiravir does not improve cure time or clinical outcomes and does not show an antiviral effect in the treatment of COVID-19 infection [2–4].

β-D-N4-hydroxycytidine (NHC, EIDD-1931) is a ribonucleoside analogue with a wide spectrum of activity against various RNA viruses [5]. Molnupiravir (MK-4482/EIDD-2801), or β-D-N4-hydroxycytidine-5'-isopropyl ether, is a biologically active NHC prodrug. It is an oral drug and is more convenient for mass administration in humans than remdesivir or other antiviral agents such as convalescent plasma and neutralizing antibodies, which require intravenous or intramuscular injection and hospital use. NHC has been shown to be effective against various RNA viruses such as influenza, Ebola virus (EBOV), Venezuelan encephalitis virus (VEEV), SARS-CoV-2, SARS-CoV, MERS-CoV and related zoonotic groups 2b or 2c Bat-CoV in *in vivo* and *in vitro* experiments [6–8]. A series of preclinical and clinical trials have proven that Molnupiravir is safe and effective for the treatment of SARS-CoV-2 infection [9, 10]. Following oral administration, Molnupiravir is rapidly converted to active NHC in plasma, distributed to various organs, and converted to the corresponding 5'-triphosphate by human kinases [11]. It is known that NHC 5'-triphosphate is a competitive substrate for viral RNA-dependent RNA polymerase, integrates into viral RNA, and leads to the accumulation of lethal mutations in the viral genome [12].

Since 2022, the new SARS-CoV-2 variant B.1.1.529 (Omicron) and its subvariants containing multiple mutations in the viral genome have dominated all over the world [13]. Mutations in the RBD domain of S-glycoprotein reduce the effectiveness of preexisting antibodies formed after infection of COVID-19 and vaccination [14]. Given the emergence of new variants of SARS-CoV-2, the aim of this study was to evaluate the efficacy of Favipiravir and Molnupiravir against different variants of SARS-CoV-2.

METHODS

Experiments were performed on the cell line Vero E6 (ATCC CRL-1586). Cells were cultured in DMEM growth medium (Gibco; USA) supplemented with 5% fetal bovine serum (FBS; HyClone, USA), 1× antimycotic antibiotic solution (Capricorn Scientific GmbH; Germany) and 1× GlutaMAX (Gibco; USA). To study the antiviral effect, various dilutions of the test compound were added to the cell monolayer and incubated for 1 h at 37 °C and 5% CO_2. After that, cells were infected with the SARS-CoV-2 at 100 $TCID_{50}$ ($TCID_{50}$ is a tissue culture dose that causes the death of 50% of the monolayer cells). In this experiment, the following variants of the SARS-CoV-2 virus were used: Wuhan B.1.1 (PMVL-4), Omicron BA.4.6 (PMVL-55), Omicron BA.5 (PMVL-52) and Omicron BA.5.2 (PMVL-54). Inhibition of the virus-induced cytopathic effect (CPE) under the action of the compound was determined by MTT test [15].

As an animal model of infection, female Syrian hamsters were used ("Stolbovaya"; Russia). Animals were kept in individually ventilated cages (temperature 21–25 °C, humidity 20%, pressure –0.1 kPa) with free access to food and water. The light regime was 12 hours of light and 12 hours of darkness. Animals were divided into experimental groups (5–8 animals each), which were orally administered Molnupiravir (200 mg/kg), Favipiravir (200–300 mg/kg), and a control group of infected animals. Animals were infected intranasally with SARS-CoV-2 strain PMVL-4 or PMVL-52 at 10^5 $TCID_{50}$. For four days, the animals were administered study drugs twice a day. On the fifth day of the experiment, the animals were euthanized by CO_2 inhalation and cervical dislocation, and lung tissues were collected at necropsy for analysis. Hamster lungs were subjected to homogenization followed by separation of the supernatant by low speed centrifugation at 12,000 rpm for 10 min. The virus titer was determined in a monolayer of Vero E6 cells. For each lung homogenate sample, the virus titer was determined after 72 hours of infection and expressed as PFU/mg lung (plaque forming units). Total RNA was isolated from lung homogenates using the ExtractRNA reagent (Evrogen; Russia) according to the manufacturer's instructions. The reverse transcription reaction was performed using a SARS-CoV-2 FRT kit for quantitative determination of SARS-CoV-2 coronavirus RNA using a panel characterized by the number of copies of the SARS-CoV-2 amplified fragment (N.F. Gamaleya National Research Center for Epidemiology and Microbiology; Russia). Results were expressed as numbers converted to log10 SARS-CoV-2 viral load per mg lung tissue.

RESULTS

At the first stage of the study, the cytotoxicity of Favipiravir and Molnupiravir on Vero E6 cells was assessed. It was found that Favipiravir has a pronounced cytotoxic effect, significantly inhibiting cell proliferation at a concentration of 1000 μM (decrease in cell viability up to 60%). At all other concentrations tested, Favipiravir showed a dose-dependent cytotoxic effect (Fig. 1). Molnupiravir had no significant effect on cell viability, inhibiting their proliferation at 200 μM by an average of 10%.

The study of the antiviral activity of Favipiravir and Molnupiravir against SARS-CoV-2 was carried out using four variants of the virus: the reference strain of the Wuhan variant (genetic line B.1.1) and three variants of the Omicron virus currently circulating in the Russian Federation, and worldwide (BA.4.6, BA.5 and BA.5.2) (Fig. 2). It was found, that at a concentration of 1000 μM, Favipiravir showed no activity against the reference strain from line B.1.1. Inhibition on ~50% at the same concentration (~160 mg/mL) was found for the BA.5 and BA.5.2 variants of the Omicron. Inhibition of the Omicron BA.4.6 virus variant did not exceed 20%. Molnupiravir showed a broad spectrum of antiviral activity,

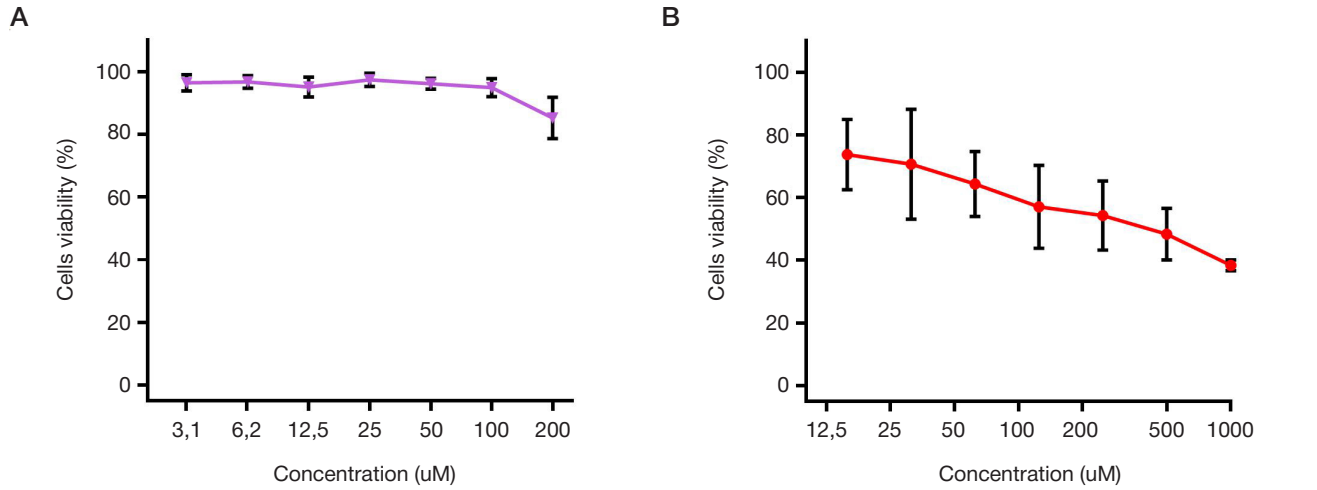

Fig. 1. Cytotoxicity study of Molnupiravir (**A**) and Favipiravir (**B**) using Vero E6 cells

inhibiting all virus variants used with IC_{50} values from 16.51 to 7.88 μM.

Further, the effectiveness of the drugs was investigated using an infectious animal model. Syrian hamsters were treated with 300 mg/kg Favipiravir or 200 mg/kg Molnupiravir via oral gavage. The animals were then infected intranasallywith the SARS-CoV-2 Wuhan variant. The drugs were given to the animals twice a day for four days. During infection, animals from the infected control group lost more than 20% weight ($p < 0.01$). Animals treated with Favipiravir lost weight by 10% ($p > 0.05$), showed apathy and food refusal, which indicates the toxic effect of the drug. Animals treated with Molnupiravir gained weight during the experiment (Fig. 3). A study of SARS-CoV-2 viral load in the lungs of animals showed that both Molnupiravir and Favipiravir reduced the amount of viral RNA (1 Log10). When determining the infectious titer of SARS-CoV-2 in the lungs of animals, it was found that all drugs suppress the replication of the virus. Treatment of animals with Molnupiravir and Favipiravir significantly reduced the virus titer (~1.5 Log10). When studying the effectiveness of drugs in animals using the Omicron BA.5 virus variant, it was found that this variant is less pathogenic than the Wuhan variant. The drug were administrated with the same doses (200 mg/kg). During the experiment, the animals gained weight in all the studied groups. A decrease in viral load in the lungs by 1.5 Log10 was found for the group of animals treated with molnupiravir (EIDD-2801), however, the data are not statistically significant ($p > 0.05$; 1.5 Log10). For Favipiravir, the reduction in viral load (0.5 Log10) and viable virus titer (1 Log10) was less pronounced and was not statistically significant ($p > 0.05$).

DISCUSSION

Previous studies of the antiviral activity of Favipiravir against SARS-CoV-2 show that it has a low antiviral effect with EC50 values > 200 μM. High doses of Favipiravir have been associated with signs of toxicity in animals in drug efficacy studies [16], since in vivo Favipiravir exhibits an antiviral effect at a double dose of 300 mg/kg, with a decrease in the infectious titer of the virus in the lungs by ~ 1.5 Log10 [17] . Other studies have shown that Favipiravir exhibits activity with an EC_{50} value of ~62 μM [18]. The results of our study also point to the limited antiviral potential of Favipiravir. When Vero E6 cells were infected with the SARS-CoV-2 virus, it was found that this drug does not have antiviral activity in vitro, and also exhibits cytotoxicity. We have shown the efficacy of this drug at a dose of 300 mg/kg twice a day in an animal model of infection using a Wuhan variant. In an animal model using the Omicron variant, when using a dosage reduced to 200 mg/kg, the effect was not significant. However, changes in the behavior of animals and a decrease in their weight during treatment with Favipiravir at a dose of 300 mg/kg indicate its toxic effect and the need for further dose selection in order to combine the absence of toxicity and preservation of drug activity.

Studies using primary human cells and other cell lines have confirmed that NHC (the active metabolite of Molnupiravir) has potent antiviral activity against various coronaviruses such as SARS-CoV, SARS-CoV-2 and MERS-CoV. The IC_{50} values for molnupiravir against SARS-CoV-2 were 0.3–0.08 μM [19]. We found that Molnupiravir exhibits antiviral activity for all studied variants of the SARS-CoV-2 virus, with low

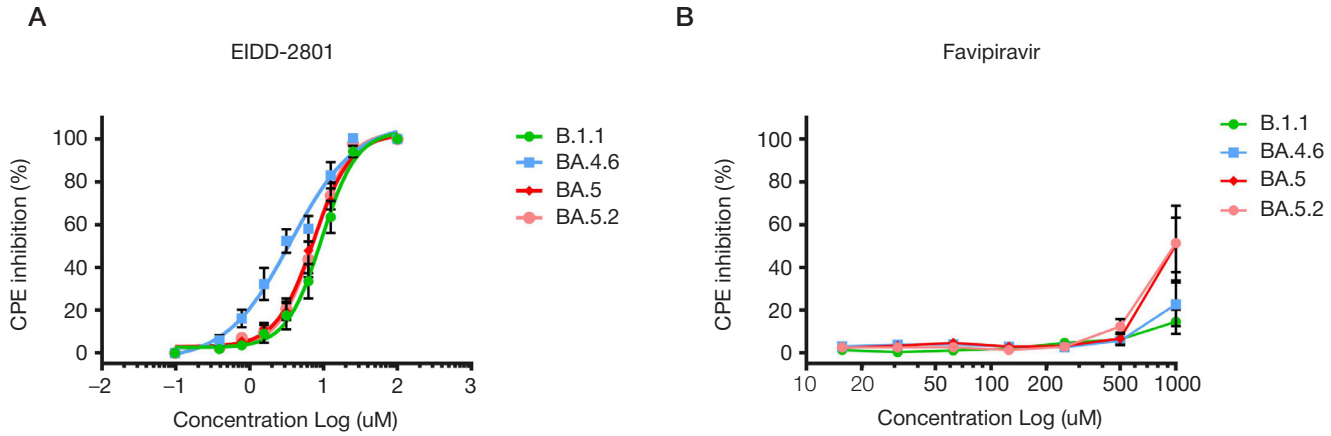

Fig. 2. Antiviral activity of Molnupiravir (EIDD-2801) (**A**) and Favipiravir (**B**) against four different variants of the SARS-CoV-2 virus

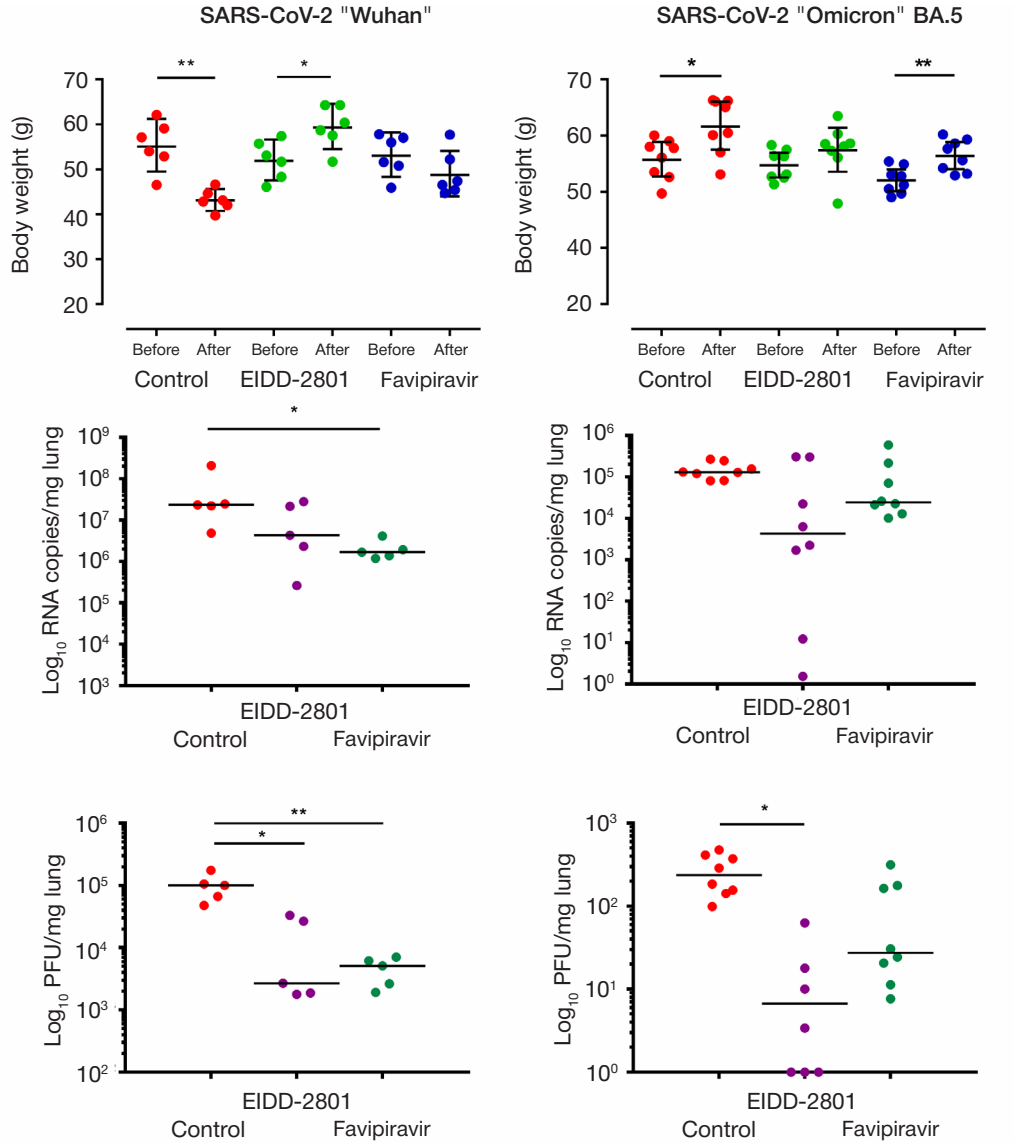

Fig. 3. The effectiveness of drugs against the Wuhan and Omicron BA.5 in animal models. Animals weight changes are presented, as well as the values of viral load and virus titer in the lungs for each animal in the corresponding group. ANOVA with Tukey's post hoc test: * — $p < 0.05$; ** — $p < 0.01$

cytotoxicity. Molnupiravir showed antiviral activity in animals infected with both Wuhan and Omicron BA.5 viruses. In a recent study, Molnupiravir also inhibited virus replication in the lungs of hamsters infected with the Omicron variant [20]. Molnupiravir significantly inhibited viral replication in the upper and lower respiratory tracts of hamsters. At the same time, the researchers found that Omicron is less pathogenic for animals compared to earlier SARS-CoV-2 genetic lines [21].

CONCLUSIONS

Favipiravir showed a rather low antiviral effect against SARS-CoV-2 at the maximum tested concentration, which had the most pronounced cytotoxic effect. Due to the pronounced cytotoxic potential and weak antiviral activity *in vitro* and *in vivo*, additional studies of the safety and efficacy of Favipiravir, dose selection, frequency of use, and clarification of indications for use are required in order to combine efficacy with minimal toxicity to the human. Molnupiravir has shown greater efficacy and safety in *in vitro* and *in vivo* models. The results for activity against the Omicron variant expand on previous data for both drugs. Further efforts are required in the search for new inhibitors and their compositions with higher specific antiviral activity. Further research is needed on the approved drugs Favipiravir and Molnupiravir in order to select the optimal treatment regimens to achieve the maximum antiviral effect.

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